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Improved Exercise Capacity With Acute Aminophylline Administration in Patients With Syndrome X

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The efficacy of the adenosine receptor blocker aminophylline on exercise capacity in patients with effort ischemia and documented coronary artery disease has been previously documented. In this study the effect of aminophylline on effort electrocardiographic (ECG) alterations and chest pain was tested in eight patients with syndrome X (anginal chest pain on effort, ischemic ECG changes during exercise, positive dipyridamole test, normal epicardial coronary arteries on angiography and absence of coronary spasm after ergonovine).

After double-blind, randomized intravenous infusion of aminophylline (6 mg/kg body weight over 15 min) or placebo (20 ml of saline solution over 15 min), the eight patients with syndrome X underwent an upright bicycle exercise stress test on 2 consecutive days. After aminophylline, there was an increase in effort tolerance (aminophylline 7.7 ± 1.2 min of exercise versus placebo 5.6 ± 0.9, $p < 0.01$) paralleled by an increase of the rate-pressure product (mm Hg × beats/min × 1/100) at 0.1 mV of ST segment depression or at peak exercise (aminophylline 278 ± 55 versus placebo 230 ± 24, $p < 0.05$). Aminophylline provoked the abolition of ECG signs of ischemia in all eight patients.

Thus, at a dosage that should effectively inhibit adenosine receptors, aminophylline infusion exerts a beneficial effect on exercise-induced chest pain and ischemia-like ECG changes in syndrome X. This effect occurs possibly through the prevention of myocardial flow maldistribution elicited by inappropriate adenosine release during effort in the presence of increased coronary resistance at the level of small intramural coronary arteries. This study, however, does not document the ischemic nature of effort-induced pain and ECG alterations in syndrome X.

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Experimental (1) and clinical (2,3) studies have recently outlined a role for primary reduction in coronary supply occurring through flow maldistribution as a mechanism of effort ischemia in patients with coronary artery disease (1,2). Transmural redistribution of flow distal to coronary stenosis during effort may be mediated by endogenous release of adenosine, which is likely to play a major role in the regulation of coronary resistance (4). In these patients, dipyridamole, which acts through an elevation of endogenous adenosine plasma levels (5) by inhibiting the uptake of adenosine across endothelial cells (6), reproduces the symptomatic, electrocardiographic (ECG) and echocardiographic signs of effort-induced ischemia (7).

Aminophylline, which acts as an antidote to dipyridamole by blocking adenosine receptors (8,9), exerts beneficial effects on exercise-induced ischemia in patients with coronary artery disease, possibly by preventing myocardial flow maldistribution elicited by excessive adenosine release during effort (10).

Recently, Cannon and Epstein (11) hypothesized that the transmural steal phenomenon might also occur in "microvascular angina." This is a clinical syndrome of effort-induced pain and ischemia-like ECG ST segment depression with a documented reduction in flow reserve, angiographically normal coronary arteries and absence of coronary spasm of large coronary arteries (syndrome X). The site of abnormally elevated resistance was proposed to be intramural, upstream from the endocardium-epicardium branching point, which is not visualized by coronary angiography (12). This abnormality would represent the anatomic background for the occurrence of the transmural steal phenomenon, triggered by arteriolar vasodilation achieved by metabolic or pharmacologic stimuli (13,14), although no clear-cut evidence exists of the ischemic nature of pain and ECG

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Table 1. Hemodynamic Data in Eight Patients in Rest Conditions and After Placebo or Aminophylline Infusion Before Starting the Exercise Test

	Basal	Placebo	Basal	Aminophylline
Heart rate (beats/min)	90 ± 8	89 ± 9	91 ± 13*	107 ± 15
Diastolic blood pressure (mm Hg)	86 ± 11	86 ± 9	81 ± 11	81 ± 10
Systolic blood pressure (mm Hg)	134 ± 14	134 ± 13	128 ± 17	125 ± 15
Rate-pressure product (mm Hg × beats/min × 10^{-2})	121 ± 18	119 ± 18	116 ± 15†	135 ± 29

*$p < 0.01$; †$p < 0.05$. Values are mean ± SD.

alterations. If this were true, one would expect that blockade of the adenosine receptors, blunting excessive arteriolar dilation, might have beneficial effects on exercise capacity in these patients.

The aim of this study was to test whether aminophylline, at a dosage inhibiting adenosine receptors, might increase exercise capacity in patients with syndrome X.

Methods

Study patients. Twelve women, aged 41 to 62 years (mean 49.4), were studied; all had chest pain on effort and an abnormal exercise test limited by angina with clear-cut horizontal or downsloping ST segment depression (≥0.20 mV). All patients had angiographically normal epicardial coronary arteries and absence of even minimal luminal irregularities, presence of normal global and regional ventricular function at baseline (by ventriculography and echocardiography) and absence of coronary spasm on ergonovine testing. As an inclusion criterion, all patients also had a positive dipyridamole test, with anginal pain and ECG changes similar in type and degree to those observed during the exercise stress test, but without any sign of ventricular dysfunction detected by echocardiographic monitoring (14). In all 12 patients, the parenteral administration of aminophylline, up to 240 mg over 3 min, fully and promptly resolved symptoms and ECG abnormalities induced by dipyridamole. No patient had taken cardiac medications for ≥7 days.

No patient had left or right bundle branch block, congestive heart failure, complex ventricular arrhythmias, history of myocardial infarction, evidence of cardiomyopathy, valvular heart disease, left ventricular hypertrophy, systemic hypertension, diabetes mellitus, collagen disease, severe anemia or polycythemia. Four patients had a history of angina at rest. All patients gave informed consent to enter the study and the protocol was approved by our institution.

Study design. Patients performed two exercise stress tests on 2 consecutive days. Before each exercise test, they received in a double-blind fashion a randomly allocated infusion of placebo (20 ml of saline solution over 15 min) or aminophylline (6 mg/kg body weight over 15 min). Exercise was started at 5 min after the end of each infusion.

Exercise stress test. Patients performed two multistage bicycle ergometer tests with an initial work load of 25 W and increments of 25 W every 2 min. Electrocardiographic leads showing the most obvious ischemic changes during the previous exercise test were continuously monitored during exercise. A 12 lead ECG and systolic and diastolic pressure, obtained by a cuff sphygmomanometer, were continuously recorded. Criteria for interrupting the test were 1) ≥0.2 mV ST segment depression 0.08 s after the J point, or 2) maximal age-related heart rate, moderately severe chest pain or muscular exhaustion in the absence of ischemia, alone or in combination.

The rate-pressure product (heart rate × systolic blood pressure × 10^{-2}) was used as an index of heart work (15) and measured at the onset of ischemia (arbitrarily fixed at 0.10 mV of ST depression) or, in negative tests, at peak exercise.

Statistical analysis. Values are expressed as mean values ±1 SD. Statistical significance was evaluated by the Student *t* test for paired values and by chi square test. A p value <0.05 was considered significant.

Results

Of the 12 patients, 4 were excluded from the study because side effects occurred during aminophylline infusion: hypotension (decrease in diastolic blood pressure >30 mm Hg) in 2, chest pain in 1 and asymptomatic ventricular trigeminy in 1. In all cases, side effects promptly disappeared when the aminophylline infusion was stopped.

Rest conditions. In the eight patients who completed the study, after placebo infusion there was no significant change from the control value in heart rate, systolic blood pressure or rate-pressure product. After aminophylline, a slight increase in heart rate was recorded (Table 1).

Exercise testing. All eight exercise tests were positive by ECG criteria after placebo; none was positive after amino-

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phylline ($p < 0.01$). Seven patients experienced anginal pain during the placebo test, and in three of them pain was abolished during the test with aminophylline infusion.

In comparison with placebo, aminophylline effected a significant increase in duration of exercise (7.7 ± 1.2 versus 5.6 ± 0.9 min, $p < 0.01$). The rate-pressure product recorded at peak exercise (in negative tests) or at 0.1 mV of ST segment depression was also significantly higher after aminophylline (278 ± 55 versus 230 ± 24, $p < 0.05$).

Discussion

Aminophylline in syndrome X. Aminophylline infusion, at a dosage effectively blocking adenosine receptors, increased the effort tolerance and ischemic threshold in eight patients with syndrome X. This finding is of pathophysiologic and potential clinical interest. A major problem of all studies in patients with a history of chest pain in the absence of angiographically assessed coronary artery disease is the assumption of homogeneity of cause in all subjects (16): it seems unlikely that a syndrome defined in this way would have a unique etiology. Therefore, in this study, restrictive criteria were adopted to identify a homogeneous subset of patients with "syndrome X." Although the ischemic origin of chest pain and related ECG changes in these patients is still debated, being favored by some authors (11–14,17) but rejected by others (18) in spite of the common finding of a reduced coronary reserve, we thought it worthwhile to test the effect of aminophylline.

Reduced flow reserve in syndrome X. In these patients with reproducible stress-induced ischemic ECG changes, the presence of dipyridamole-induced chest pain or ST segment depression, or both, reliably identifies a reduction in flow reserve (12,19). Epstein and Cannon (20) have hypothesized that an abnormally elevated resistance to flow at the level of the small intramural coronary arteries, upstream from the endocardium-epicardium bifurcation, might induce a subendocardial steal. According to their hypothesis, the abnormal resistance to flow would result in maximal dilation of the subendocardial arterioles in the rest condition (and in the absence of pharmacologic vasodilator stimuli) because of the concomitant higher metabolic demand of the subendocardium. The putative mechanism of the steal as a response to pharmacologic or metabolic stimuli, such as dipyridamole and pacing or exercise, would be related to the inability of the subendocardial arterioles to dilate further versus a "normal" dilation of the subepicardial arterioles and the consequent decrease in pressure downstream from the site of increased resistance, with reduction of flow to the subendocardium.

Mechanism of aminophylline's action. Adenosine, which plays a major role in regulating coronary resistance, could be the trigger of the transmural steal after effort or dipyridamole administration. At the dosage employed in this study, aminophylline effectively inhibits adenosine receptors and, according to experimental data, should not elicit $beta_2$-adrenergic stimulation. Aminophylline might exert an antisteal action blunting adenosine-mediated excessive hyperemia, which would result in a transmural coronary steal with detrimental underperfusion of the subendocardium. Also, the stimulation of $alpha_1$-adrenergic receptors might contribute to the phenomenon of reverse transmural steal (21–23). That mechanism would involve coronary alpha constriction, lower coronary flow velocity, diminish pre-arteriolar gradients and, therefore, increase perfusion pressure distal to the site of elevated resistance, resulting in increased transmural perfusion.

Clinical implications. The finding of this study on the effect of aminophylline may have clinical implications because aminophylline is also available in oral formulation and some patients with syndrome X respond poorly to conventional medical treatment (24). Although our results are compatible with the hypothesis of a transmural steal in syndrome X, the actual ischemic nature of pain and ECG alterations in these patients remains to be established.

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